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Incidence of hepatocellular carcinoma in nonalcoholic fatty liver disease without cirrhosis or advanced liver fibrosis

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Abstract

Background: HCC can develop in the absence of cirrhosis in patients with NAFLD. We aimed to estimate the incidence of HCC in patients with NAFLD with and without cirrhosis or advanced liver fibrosis.

Methods: We performed a cohort study to determine the incidence of HCC in patients with NAFLD identified by the International Classification of Diseases 9/10 codes in the electronic health records of a US health care system between 2004 and 2018. The incidence of HCC was stratified by the presence or absence of cirrhosis and by the Fibrosis-4 index (FIB-4) at the time of HCC diagnosis.

Results: Of 47,165 patients with NAFLD aged 40–89 years, 981 (2.1%) developed HCC (mean follow-up 3.4 y). Among patients with HCC, 842 (85.8%) had cirrhosis, while 139 (14.2%) did not. Of the 139 patients with HCC without cirrhosis-related diagnostic codes, 26 (2.7%) had FIB-4 >2.67 (advanced fibrosis likely), whereas 43 (4.4%) had FIB-4 <1.30 (excluding advanced fibrosis). The annual incidence of HCC in patients with NAFLD with and without cirrhosis was 23.6 and 1.1 per 1000 person-years, respectively. Among patients without cirrhosis, the annual incidence of HCC was 2.8 per 1000 person-years with FIB-4 >2.67 and 0.7 per 1000 person-years with FIB-4 <1.30. Patients with NAFLD and cirrhosis were 31.8 times (95% CI, 23.3–43.4) more likely to develop HCC than those without cirrhosis and FIB-4 <1.30, after adjustment for age and sex.

Conclusions: Patients with NAFLD without cirrhosis nor advanced fibrosis have a low incidence of HCC.

Abbreviations: ALT, alanine aminotransferase; ALBI, albumin-bilirubin index; ALP, alkaline phosphatase; AST, aspartate aminotransferase; BMI, body mass index; cACLD, compensated advanced chronic liver disease; FIB-4, fibrosis-4 index;HER, electronic health record; ICD, International Classification of Diseases; INR, international normalized ratio.

Preliminary results of this study were presented as an oral presentation at the American Association for the Study of Liver Diseases Annual Meeting on November 2021.

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INTRODUCTION

Due to the high global prevalence of NAFLD, HCC associated with NAFLD is emerging as a major public health issue.[1–3] Furthermore, metabolic syndromes, including diabetes mellitus, hyperlipidemia, and hypertension, which commonly coexist with NAFLD, incur additional risk for HCC development.[4] In the United States, the incidence of NAFLD-related HCC is projected to increase by up to 120% by 2030.[1] NAFLD with cirrhosis portends a high risk of HCC, with a reported cumulative incidence of up to 12.8% with 3.2 years of follow-up.[5] Hence, practice guidelines recommend surveillance for HCC in patients with NAFLD with cirrhosis.[6]

However, HCC can also arise in patients with NAFLD without preexisting cirrhosis.[7] There is uncertainty regarding the incidence of HCC in NAFLD without cirrhosis, with estimates ranging from 0% to 38% within 10 years of follow-up.[8] Given the significant inconsistency in available evidence, no consensus exists regarding the optimal HCC surveillance strategy in patients with NAFLD without cirrhosis. This gap in knowledge has important implications in the clinical management of NAFLD, given the high prevalence and underdiagnosis of this condition in the general population, and the clinical challenge of determining advanced fibrosis without a liver biopsy.[9–11] Thus, determining the incidence of HCC in patients with NAFLD stratified by the presence or absence of cirrhosis and by liver fibrosis stage remains an unmet clinical need.

In this study, we investigated the incidence of HCC in patients with NAFLD using electronic health record (EHR) data from a large US-based health care system. We aimed to determine the incidence of HCC in patients with NAFLD with or without cirrhosis and identify risk factors associated with HCC development in NAFLD without cirrhosis or advanced liver fibrosis.

METHODS

Study setting

This retrospective cohort study included patients with NAFLD seen at any of the facilities of UPMC, a large health care network, including tertiary care hospitals, community hospitals, specialty clinics, and primary care centers in the Mid-Atlantic United States, between January 2004 and December 2018. Visit encounters at both inpatient and/or outpatient centers were evaluated. International Classification of Diseases (ICD) codes versions 9 and 10 were used to identify the study population.[12–14] The data were captured by a computer-based algorithm search of EHRs. All patients were evaluated by the institution's master patient index to ensure that patients with multiple medical records were assigned by only one identifier to eliminate multiple counts. For each patient, the date of the first encounter coded with NAFLD was used as the time of entry into the study. The date of the last contact in the UPMC network was recorded to determine the follow-up duration. The date of the first encounter coded with HCC was recorded.

Ethics statement

All research was conducted in accordance with both the Declarations of Helsinki and Istanbul. The study was approved by the University of Pittsburgh Human Research Protection Office as a consent-waived study (STUDY19010189). Deidentified patient data were obtained through a health record research request through the University of Pittsburgh Department of Biomedical Informatics.

Identification of patients with NAFLD with and without cirrhosis and/or HCC

We utilized the 2021 expert panel consensus guidelines on research using EHR-based administrative data to define NAFLD, cirrhosis, and HCC.[15] The eligibility criteria for the NAFLD cohort were age between 40 and 89 years and diagnosed with either NAFL, NASH, and cirrhosis of liver without mention of alcohol (see ICD codes in Supplemental Table S1, http://links.lww.com/HC9/A389). The diagnosis of compensated/decompensated cirrhosis associated with NAFLD was based on ICD-9/10 codes, as outlined in Supplemental Table S1, http://links.lww.com/HC9/A389. Exclusion criteria were patients with any of the following diagnoses: alcohol-associated liver disease, alcohol use disorder, somatic consequences of alcohol, autoimmune liver disease, alpha-1-antitrypsin deficiency, secondary or unspecified biliary cirrhosis, drug use disorder except nicotine/caffeine, hemochromatosis, Budd-Chiari syndrome, viral hepatitis, unspecified chronic hepatitis, or Wilson disease (see ICD codes in Supplemental Table S2, http://links.lww.com/HC9/A389). The primary outcome of the study was the diagnosis of HCC between January 1, 2004, and December 31, 2018. All HCC cases were identified based on ICD-9 code 155.0 or ICD-10 codes C22.0 and C22.8.

Data collection

Data on demographics, comorbid conditions, and laboratory markers were extracted from the EHR. The baseline time for entry to the study was defined as the index encounter for the initial diagnosis of HCC or NAFLD for each patient. Baseline body mass index (BMI) was extracted from the index encounter. Comorbid conditions, including diabetes mellitus, hyperlipidemia, and hypertension, were recorded as being present if coded for at least once from the index encounter to the date of HCC diagnosis, death, or the last encounter, whichever occurred first. The laboratory measurements, including the calculation of noninvasive fibrosis scores and when data from multiple time points were available during the study period, were recorded from the closest time point before HCC diagnosis.

We used several noninvasive markers of liver fibrosis, including the aspartate aminotransferase/$\sqrt{\text{alanine aminotransferase}}$ (AST/$\sqrt{}$ALT) ratio, the albumin-bilirubin index (ALBI), and the Fibrosis-4 index (FIB-4). The ALBI score was calculated based on the formula: ALBI score $= -0.085 \times$ (albumin g/L) + $0.66 \times$ lg(TBil μmol/L).[16] The FIB-4 was calculated as follows [(age[years] × AST [U/L])/(platelet [10^9/L] ×$\sqrt{}$ALT [U/L])].[17] The AST/$\sqrt{}$ALT ratio was previously shown as a marker of fibrosis in patients with NAFLD,[18] and the ALBI score was a discriminatory factor in the liver function and prognosis in patients with HCC.[16] Among biochemistry-based noninvasive tests to assess the fibrosis stage, FIB-4 has been validated to estimate fibrosis in patients with NAFLD and found to be superior to other noninvasive markers.[19] The cutoffs of FIB-4 were <1.3 (low risk), 1.3–2.67 (indeterminant risk), and >2.67 (high risk for advanced fibrosis.[20]

Statistical analysis

Continuous variables were described with mean and SD, whereas categorical variables were described with frequency. When comparing the clinical characteristics of patients diagnosed with HCC without cirrhosis or advanced fibrosis to patients with HCC and cirrhosis or advanced fibrosis, the student *t* test was used for continuous variables and the chi-squared test for categorical variables. We used the same statistical methods for comparing the characteristics of patients with NAFLD with or without HCC. The average annual incidence rates of HCC in patients with NAFLD with or without cirrhosis or different categories of risk for liver fibrosis were estimated using the Poisson regression model with an offset for the years of the follow-up period. Statistical analyses were carried out using SAS software version 9.4 (SAS Institute, Cary, NC). All *p*—values reported are 2-sided. The *p*—values of <0.05 were considered to be statistically significant. The study flow diagram was created with BioRender.com.

RESULTS

Baseline characteristics of the study cohort

The present analysis included 47,165 patients with the diagnosis of NAFLD, with total of 163,845.88 person-years of follow-up (Figure 1). The mean (SD) values of age at baseline and BMI of the entire NAFLD cohort were 60.0 (11.5) years and 33.6 (7.5) kg/m^2, respectively. Among these patients, 56.5% were women, 48.2% were ever smokers, 46.7% had a history of diabetes, 75.8% had a history of hypertension, and 59.3% had a history of dyslipidemia (Table 1).

Incidence of HCC in patients with NAFLD with or without cirrhosis

In the entire cohort, 9840 (20.9%) had a clinical diagnosis of cirrhosis before or concurrent with the diagnosis of HCC, whereas the remaining 37,325 (79.1%) did not have a diagnosis of cirrhosis. After an average of 3.4 years of follow-up, 981 patients developed HCC, of whom 842 patients had a clinical diagnosis of cirrhosis, while 139 did not. The average incidence rates of HCC in patients with NAFLD with and without cirrhosis were 22.5 (95% CI, 20.8–24.3) and 1.1 (95% CI, 0.9–1.1) per 1000 person-years, respectively, with adjustment for age and sex (Table 2). Patients with NAFLD with cirrhosis were >20 times (rate ratio = 21.3, 95% CI, 17.7–25.5) more likely to develop HCC than patients with NAFLD without cirrhosis.

Incidence of HCC in patients with NAFLD without cirrhosis stratified by FIB-4 score

Among 37,325 patients with NAFLD without cirrhosis, 2801 (7.5%) had an FIB-4 score of >2.67 (high risk for advanced fibrosis), 10,931 (29.3%) had an FIB-4 score between 1.30 and 2.67 (indeterminate risk), 17,634 (47.2%) had an FIB-4 score of <1.30 (low risk for advanced fibrosis), and the remaining 5959 (16.0%) had missing FIB-4 values (Table 2). Among patients with NAFLD without cirrhosis, the average incidence rates (per 1000 person-years) of HCC for patients with FIB-4 < 1.30, 1.30–2.67, and >2.67 were 0.7 (95% CI, 0.5–1.0), 1.2 (95% CI, 0.8–1.5), and 2.8 (95 CI, 1.9–4.0), respectively (Table 2). The risk of

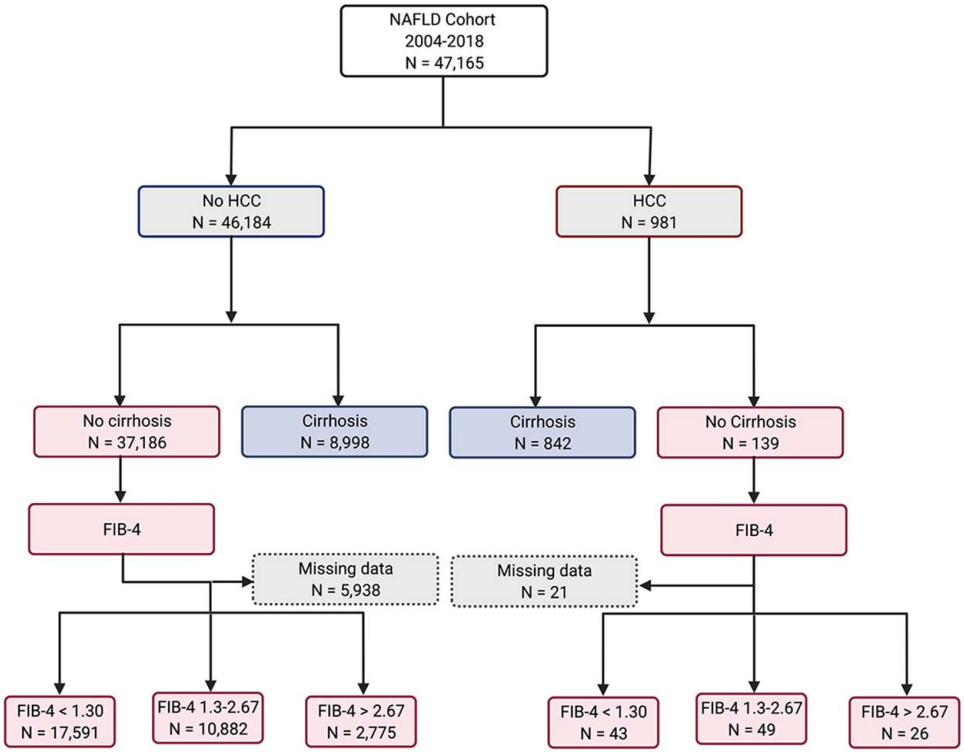

FIGURE 1 Flow diagram of the patient cohort used in the analysis. Abbreviation: FIB-4, Fibrosis-4 index.

HCC for patients with NAFLD with FIB-4 < 1.30 was ~4 times lower (rate ratio = 0.26, 95% CI, 0.16–0.42) than for patients with FIB-4 > 2.67 without overt cirrhosis and > 30 times lower (rate ratio = 0.03, 95% CI, 0.02–0.04) than those with cirrhosis.

A lower FIB-4 cutoff of 2 has been proposed for ruling out advanced fibrosis in patients with NAFLD > 65 years.[21] Therefore, we also analyzed the data using this age-adjusted FIB-4 cutoff in patients without cirrhosis and found that the annual incidence rate was slightly higher (0.8 vs. 0.7 per 1000 person-years) in the low-risk FIB-4 group and lower (1.1 vs. 1.2 per 1000 person-years) in the indeterminate FIB-4 group (Supplemental Table S3, http://links.lww.com/HC9/A389).

In clinical practice, it is often difficult to differentiate NAFLD with advanced fibrosis from compensated cirrhosis, and the term compensated advanced chronic liver disease has been proposed, which includes both these entities.[22] Accordingly, the relative risk of HCC in patients diagnosed with cirrhosis and FIB-4 > 2.67 (ie, patients with compensated advanced chronic liver disease) was 31.62 (95% CI, 23.08–43.32) compared with inpatients without cirrhosis and FIB-4 < 1.30, after adjustment for age and sex.

Clinical characteristics of patients with NAFLD-HCC with or without cirrhosis

Among patients with HCC, those without cirrhosis and FIB-4 < 1.30 were younger and less likely to have diabetes and had lower values of AST, ALT, alkaline phosphatase, international normalized ratio, total bilirubin, ALBI and AST/$\sqrt{}$ALT ratio, and higher platelet count compared with patients with HCC with cirrhosis or FIB-4 > 2.67 (all p's < 0.05) (Table 3). There was no statistically significant difference between the 2 groups by sex, race, history of smoking, and hypertension, as well as in values of BMI and glucose (Table 3). After the age-adjustment of the lower cutoff of FIB-4 score for patients above 65 years to 2 instead of 1.3, sex was additionally significantly different between the 2 groups (Supplemental Table S4, http://links.lww.com/HC9/A389).

Clinical characteristics of patients with NAFLD without cirrhosis/nonadvanced fibrosis patients with NAFLD with or without HCC

Next, we compared the clinical characteristics of patients with NAFLD with or without a diagnosis of HCC among those without cirrhosis or advanced fibrosis (ie, FIB-4 < 1.30). Patients with NAFLD-HCC without cirrhosis or advanced fibrosis had lower BMI and albumin but higher alkaline phosphatase, platelet count, ALBI, and AST/$\sqrt{}$ALT ratio (Table 4). There was no statistically significant difference between the two groups by age, sex, race, history of smoking, diabetes, and hypertension, as well as ALT, glucose, total bilirubin, and FIB-4 score (Table 4). Adjustment of the lower FIB-4 cutoff to 2 for age above

TABLE 1 Characteristics of patients with NAFLD with or without HCC

Characteristic[a]	HCC		Non-HCC		p[b]
	Total N	N (% of total N)	Total N	N (% of total N)	
Number (%)					
Female	981	429 (43.7)	46,184	26,235 (56.8)	<0.001
White	953	903 (94.8)	45,459	42,284 (93.0)	0.037
Ever smokers	705	397 (56.3)	41,259	19,828 (48.1)	<0.001
Had diabetes	981	578 (58.9)	46,184	21,449 (46.4)	<0.001
Had hypertension	981	808 (82.4)	46,184	34,925 (75.6)	<0.001
Had hyperlipidemia	981	429 (43.7)	46,184	27,537 (59.6)	<0.001
Mean (SD)					
Age (y)	981	68.1 (10.4)	46,184	63.3 (11.4)	<0.001
BMI (kg/m^2)	749	30.7 (6.8)	42,258	33.3 (7.0)	<0.001
AST (U/L)	818	86.2 (174.8)	42,068	52.3 (363.0)	0.008
ALT (U/L)	839	64.9 (105.8)	42,379	46.1 (148.1)	<0.001
ALP (U/L)	809	203.7 (223.7)	42,154	99.2 (98.0)	<0.001
INR	816	1.26 (0.46)	31,537	1.25 (0.67)	0.604
Platelet count (×10^3/μL)	856	199.8 (119.1)	41,015	222.9 (85.6)	<0.001
Total bilirubin (mg/dL)	827	2.01 (3.86)	42,010	0.95 (2.24)	<0.001
Albumin (g/dL)	825	3.37 (0.71)	42,187	3.77 (0.81)	<0.001
FIB-4 score[c]	800	4.98 (6.25)	39,303	3.21 (22.45)	0.026
ALBI score[d]	803	−2.05 (0.75)	41,738	−2.54 (0.75)	<0.001
AST/$\sqrt{}$ALT ratio	816	10.16 (11.92)	42,028	5.91 (12.40)	<0.001
Glucose (mg/dL)	814	140.0 (67.6)	43,154	125.3 (131.2)	0.002

[a]Data collected before cancer diagnosis for HCC or last encounter for non-HCC.
[b]Derived from χ^2 test and *F* test.
[c]FIB-4 = age (year) × AST (U/L) / [PLT (10^9/L) × ALT$^{1/2}$ (U/L).
[d]ALBI = $\log_{10}$ total bilirubin (μmol/L) × 0.66 + albumin (g/L) × (−0.085).
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; FIB-4, Fibrosis-4 index; INR, international normalized ratio.

65 years showed similar results, except that AST was additionally significantly different between the groups (Supplemental Table S5, http://links.lww.com/HC9/A389).

TABLE 2 Distribution of cirrhosis and FIB-4 scores among patients with NAFLD with or without HCC and corresponding annual incidence rate of HCC

	HCC N (%)	Non-HCC N (%)	Rate per 1000 person-years
All subjects	981 (100)	46,184 (100)	6.0
Diagnosis of cirrhosis			
Yes	842 (85.8)	8998 (19.5)	22.5[a]
No	139 (14.2)	37,186 (80.5)	1.1[a]
FIB-4[b] score among subjects without cirrhosis			
<1.30	43 (4.4)	17,591 (38.1)	0.7[c]
1.30–2.67	49 (5.0)	10,882 (23.6)	1.2[c]
>2.67	26 (2.7)	2775 (6.0)	2.8[c]
Unknown	21 (2.1)	5938 (12.8)	1.2[c]

[a]Rates were adjusted for age and sex.
[b]FIB-4 = age (year) × AST (U/L) / [PLT (10^9/L) × ALT$^{1/2}$ (U/L).
[c]Rates were adjusted for sex only since age was a component of FIB-4 score.
Abbreviations: FIB-4, Fibrosis-4 index; INR, international normalized ratio.

DISCUSSION

Given the projected worldwide increase in HCC incidence attributable to NAFLD, our study provides several clinically relevant insights. First, we report that the cumulative incidence of HCC in patients with NAFLD based on EHR data from a large health care network in the United States was 2.1% with a mean of 3.4 years of follow-up. Second, we found that 14.2% of NAFLD-related HCC developed in patients without a cirrhosis diagnosis. Third, the annual incidence rate of HCC in NAFLD with cirrhosis was 2.25% but significantly lower at 0.11% in NAFLD without cirrhosis. Fourth, among patients with NAFLD without cirrhosis, the annual incidence of HCC varied by the FIB-4 score, which is a surrogate for liver fibrosis, ranging from 0.28% in the high-risk group to just 0.07% in the low-risk group. Fifth, we found some differences in clinical characteristics of patients with NAFLD without cirrhosis with HCC compared with those without HCC, suggesting potential differences in underlying disease biology. Taken together, our results suggest that an FIB-4-based risk stratification for HCC surveillance may be a useful strategy in NAFLD management, pending

TABLE 3 Characteristics of patients with HCC who did not have cirrhosis or advanced fibrosis compared with patients with HCC who had cirrhosis and/or advanced fibrosis

	HCC with no cirrhosis and FIB-4 < 1.3		HCC with cirrhosis and/or FIB-4 > 2.67		
Characteristic[a]	**Total N**	**N (% of total N)**	**Total N**	**N (% of total N)**	***p***[b]
Number (%)					
Female	43	24 (55.8)	868	366 (42.2)	0.078
White	43	42 (97.7)	842	793 (94.2)	0.333
Ever smokers	39	18 (46.2)	607	349 (57.5)	0.166
Had diabetes	43	18 (41.9)	868	521 (60.0)	0.018
Had hypertension	43	34 (79.1)	868	716 (82.5)	0.566
Had hyperlipidemia	43	21 (48.8)	868	369 (42.5)	0.413
Mean (SD)					
Age (y)	43	59.3 (9.8)	868	68.6 (10.2)	<0.001
BMI (kg/m^2)	37	31.5 (6.5)	651	30.5 (6.8)	0.412
AST (U/L)	43	24.7 (10.8)	722	93.5 (184.7)	0.015
ALT (U/L)	43	34.3 (15.7)	742	68.0 (111.5)	0.048
ALP (U/L)	41	126.6 (91.8)	715	212.1 (230.8)	0.018
INR	42	1.12 (0.25)	718	1.28 (0.47)	0.030
Platelet count (×10^3/μL)	43	318.5 (196.9)	755	191.1 (112.2)	<0.001
Total bilirubin (mg/dL)	43	0.62 (0.30)	730	2.19 (4.07)	0.012
Albumin (g/dL)	43	3.68 (0.61)	727	3.32 (0.72)	0.001
FIB-4 score[c]	43	0.90 (0.29)	708	5.45 (6.50)	<0.001
ALBI score[d]	43	−2.49 (0.53)	706	−1.99 (0.76)	<0.001
AST/$\sqrt{}$ALT ratio	43	4.32 (1.31)	721	10.8 (12.5)	<0.001
Glucose (mg/dL)	42	132.6 (50.4)	716	140.7 (69.2)	0.457

[a]Data collected before cancer diagnosis for HCC or last encounter for non-HCC.
[b]Derived from χ^2 test and *F* test.
[c]FIB-4 = age (year) × AST (U/L) / [PLT (10^9/L) × ALT$^{1/2}$ (U/L).
[d]ALBI = $\log_{10}$ total bilirubin (μmol/L) × 0.66 + albumin (g/L) × (−0.085).
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; FIB-4, Fibrosis-4 index; INR, international normalized ratio.

the development of more accurate noninvasive biomarkers of liver fibrosis.

Surveillance of high-risk patients is a crucial strategy for early detection of HCC and is associated with improved outcomes.[23] The decision to enroll a specific group of patients into a surveillance program mainly depends on the cost-effectiveness of the surveillance strategy, which, in turn, is driven by the incidence rate of HCC. The American Association for the Study of Liver Diseases guidelines recommend an annual incidence of HCC ≥ 1.8% as the cutoff to reach cost-effectiveness for surveillance.[6] Our results highlight significant differences in HCC incidence in patients with NAFLD stratified by FIB-4 score. Our results also support the current recommendations that the standard of care surveillance for HCC may not be cost-effective in patients with NAFLD without cirrhosis. However, further studies focusing on cost analysis of patients with NAFLD without cirrhosis and high FIB-4 are warranted to confirm the need for surveillance in this intermediate-risk group of patients. On the other hand, the incidence of HCC in patients with NAFLD without cirrhosis and low FIB-4 is very low; thus, regular surveillance may not be justifiable until highly sensitive and specific, and low-cost screening tools become available.[24,25]

The incidence of HCC has been estimated in several prior population-based studies. In a study from Europe, the incidence of HCC was 0.57 per 1000 person-years in NAFLD and 1.3 per 1000 person-years in NASH.[26] In a study of histologically confirmed NAFLD in Sweden, the overall HCC rate was 1.2 per 1000 person-years but varied with the advancing stage of the NAFLD (per 1000 person-years): 0.8 in simple steatosis, 1.2 in NASH without fibrosis, 2.3 in fibrosis (F1-F3) without cirrhosis, and 6.2 in cirrhosis.[27] In a Japanese cohort of patients with NAFLD, the annual incidence of HCC was 0.4 per 1000 person-years.[28] A study from the US Veterans Health Administration found the annual incidence of HCC in NAFLD, defined as elevated liver function tests in the absence of viral hepatitis, to be 0.21 per 1000 person-years.[29] Based on the studies with available histologic data, the liver fibrosis stage is the major predictor of NAFLD-related HCC in patients without cirrhosis.[30,31] Our study adds to the understanding of

TABLE 4 Characteristics of patients with or without HCC among patients with NAFLD who did not have cirrhosis or advanced fibrosis (FIB-4 < 1.30)

Characteristic[a]	HCC		Non-HCC		p[b]
	Total N	N (% of total N)	Total N	N (% of total N)	
Number (%)					
Men	43	19 (44.2)	17,591	6892 (39.2)	0.502
White	43	42 (97.7)	17,448	16,189 (92.8)	0.215
Ever smokers	39	18 (46.2)	16,813	7936 (47.2)	0.896
Had diabetes	43	18 (41.9)	17,591	7493 (42.6)	0.922
Had hypertension	43	34 (79.1)	17,591	12,996 (73.9)	0.439
Had hyperlipidemia	43	21 (48.8)	17,591	10,925 (62.1)	0.073
Mean (SD)					
Age (y)	43	59.3 (9.8)	17,591	58.4 (9.8)	0.536
BMI (kg/m^2)	37	31.5 (6.5)	17,004	34.3 (6.9)	0.013
AST (U/L)	43	24.7 (10.8)	17,591	22.2 (9.9)	0.087
ALT (U/L)	43	34.3 (15.7)	17,591	33.8 (25.3)	0.913
ALP (U/L)	41	126.6 (91.8)	17,515	85.4 (67.4)	< 0.001
INR	42	1.12 (0.25)	11,961	1.10 (0.38)	0.781
Platelet count (×10^3/μL)	43	318.5 (196.9)	17,591	268.6 (74.0)	< 0.001
Total bilirubin (mg/dL)	43	0.62 (0.30)	17,500	0.57 (0.34)	0.390
Albumin (g/dL)	43	3.68 (0.61)	17,514	3.92 (0.61)	0.013
FIB-4 score[c]	43	0.90 (0.29)	17,591	0.88 (0.24)	0.608
ALBI score[d]	43	−2.49 (0.53)	17,476	−2.71 (0.52)	0.005
AST/$\sqrt{}$ALT ratio	43	4.32 (1.31)	17,591	3.93 (0.97)	0.010
Glucose (mg/dL)	42	132.6 (50.4)	17,493	121.8 (50.1)	0.160

[a]Data collected prior to cancer diagnosis for HCC or last encounter for non-HCC.
[b]Derived from χ^2 test and F test.
[c]FIB-4 = age (year) × AST (U/L) / [PLT (10^9/L) × ALT$^{1/2}$ (U/L).
[d]ALBI = $\log_{10}$ total bilirubin (μmol/L) × 0.66 + albumin (g/L) × (−0.085).
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; FIB-4, Fibrosis-4 index; INR, international normalized ratio.

this problem by stratifying HCC incidence in NAFLD by the presence or absence of clinically diagnosed cirrhosis and further by the commonly used noninvasive test of liver fibrosis, the FIB-4 index, since the majority of patients with NAFLD do not undergo liver biopsy. We found that a high FIB-4 score (vs. low FIB-4) is associated with a 4-fold higher risk of HCC in patients with NAFLD without cirrhosis. We also found that using an age-adjusted lower cutoff for an FIB-4 score of 2 instead of 1.3 for patients with NAFLD above 65 years had only a marginal impact on the results. When combining patients diagnosed with cirrhosis and without cirrhosis but with FIB-4 > 2.67 (more likely to have advanced fibrosis), the risk of HCC development was > 30 times higher than in NAFLD with a low FIB-4. Thus, an FIB-4 score-based risk stratification strategy for HCC surveillance in NAFLD may be a useful approach that deserves further investigation.

Approximately 14% of NAFLD-related HCC cases in our cohort were diagnosed without a concurrent cirrhosis diagnosis. The development of HCC in NAFLD without cirrhosis has been reported in other studies, with incidence varying from 0.2–0.6 per 1000 person-years in Europe to 0.4–6.0 per 1000 person-years in Asia.[26,28] A meta-analysis of 19 studies reported that 38% of NAFLD-related HCC developed in patients without underlying cirrhosis.[7] In the US Veterans Health Administration system, NAFLD is currently the most common cause of HCC in patients with chronic liver disease without cirrhosis.[32] We found that HCC cases in NAFLD with low risk for fibrosis (ie, FIB-4 <1.30) had distinct clinical characteristics. While components of the metabolic syndrome, including diabetes mellitus and hyperlipidemia, were risk factors for the development of HCC in patients with NAFLD with cirrhosis or advanced fibrosis, these associations were not observed in patients with NAFLD with low-risk fibrosis.[4] NAFLD with low-risk fibrosis tended to have relatively unremarkable AST and ALT but higher alkaline phosphatase. The elevated alkaline phosphatase may reflect tumor effects on adjacent hepatic parenchyma rather than a biomarker of increased HCC risk in NAFLD without cirrhosis, and this finding will require prospective validation.

Our study has several limitations. This was a retrospective study in which the diagnosis of cirrhosis was based on ICD-9/10 diagnostic codes and had all the limitations and biases inherent in this type of study design. Furthermore, the data were obtained from a health care system located in the Mid-Atlantic United States, which has a predominantly white population that is less diverse than the country as a whole. It is possible that, despite the systematic exclusion of patients with diagnostic codes for any alcohol use disorder, intake of alcohol might have been underreported, thereby missing patients with dual-etiology fatty liver disease, based on the recently proposed metabolic dysfunction-associated fatty liver disease nomenclature.[33] Estimation of liver fibrosis in NAFLD without cirrhosis was based on the FIB-4 score and was not histologically confirmed, and scores in the indeterminate range likely represented a spectrum of liver fibrosis. There are no standardized imaging criteria for the diagnosis of cirrhosis, which may have impacted the classification of patients into the categories of the presence or absence of cirrhosis. Finally, as individual pathology reports were not available for confirmation of HCC diagnosis, it is possible that non-HCC liver tumors may have been miscoded as HCC, particularly in patients without cirrhosis who have a low pretest probability of HCC.

However, several strengths of our study should also be noted. First, we obtained data from a large cohort of patients with NAFLD in both inpatient and outpatient settings, representative of real-world clinical practice. Second, despite a cohort with a relatively large sample size, few patients had missing data, thereby minimizing the risk of selection bias. Third, most patients had laboratory values for calculating the FIB-4 score, which is widely used in clinical practice for noninvasive risk stratification of liver fibrosis in NAFLD. Fourth, we utilized validated definitions based on expert consensus to identify patients with NAFLD, cirrhosis, and HCC from administrative data, optimizing the generalizability of our findings. Finally, our results provide insights into population-level HCC risk in NAFLD patients with compensated advanced chronic liver disease, an entity that includes advanced fibrosis and compensated cirrhosis, as it is often difficult to determine the progression from advanced fibrosis to cirrhosis in clinical practice.

In conclusion, we found that the incidence of HCC in NAFLD without cirrhosis is low. Furthermore, among patients with NAFLD without cirrhosis, the HCC incidence rate varied by liver fibrosis, as determined by the noninvasive FIB-4 index, and patients with NAFLD with HCC had clinical differences compared to patients with NAFLD without HCC. Our results provide insights that may inform emerging recommendations regarding HCC surveillance in the large NAFLD population without cirrhosis.

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CONFLICTS OF INTEREST

Jaideep Behari has received research grant funding from Gilead, Pfizer, AstraZeneca, and Endra Life Sciences. His institution has research contracts with Intercept, Pfizer, Galectin, Exact Sciences, Inventiva, Enanta, Shire, Gilead, Allergan, Celgene, Galmed, Rhythm, and Genentech. The remaining authors have no conflicts to report.

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